## REMARKS

### I. Amendments to the Title and Claims

The title and claim 23 have been amended to clearly define the subject matter of the invention. The claims are supported by the originally filed specification, for example, page 5, lines 12-19, page 9, lines 7-9 and page 21, lines 3-9. No new matter has been added. Claims 1-22, 24-26, 30-72 have been canceled without prejudice. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional applications.

Claims 73-76 have been added. Allowable claim 34 has been rewritten in independent claim 73 including all of the limitations of the base claim, as suggested by the examiner. The claims are supported by canceled claims 34-39 and the originally filed specification, for example, page 5, lines 12-19, page 9, lines 7-9 and page 21, lines 3-9.

Claims 23, 27-29 and 73-76 are pending. Applicant respectfully submits that the pending claims are allowable for the following reasons.

### II. Arguments and Response to Rejections

#### The Rejection under 35 U.S.C. § 112, Second Paragraph Should be Withdrawn

Claims 23, 25-31, 33, 35-40, 59-62, and 71-72 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite in the recitation of "blood-borne tumors." (pages 4-5 of Office Action). The PTO contends that the term cannot be discerned, and thus the metes and bounds of the claims are unclear. Applicant disagrees that the claims are indefinite, for the following reasons.

A claim is definite under 35 U.S.C. 112, second paragraph if "those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576 (Fed. Cir. 1986). Claim 23 has been amended to recite "a method for treating blood-borne tumors in a patient having the blood-borne tumors comprising orally administering to said patient a capsule comprising thalidomide." The claim is definite when read in light of the instant specification. For example, the specification at page 5, lines 12-19 states as follows:

> "It should be noted that angiogenesis has been associated with blood-borne tumors such as leukemias, any of various acute or chronic neoplastic diseases of the bone marrow in which unrestrained proliferation of white blood cells occurs, usually

accompanied by anemia, impaired blood clotting, and enlargement of the lymph nodes, liver, and spleen. It is believed that angiogenesis plays a role in the abnormalities in the bone marrow that give rise to leukemia-like tumors."

Also, the specification at page 9, lines 7-9 states as follows:

"It is yet another object of the present invention to provide a method and composition for the treatment of blood-borne tumors such as leukemia."

In view of the disclosure of the application, one of ordinary skilled in the art would understand what "blood-borne tumor" means and the scope of the claims. Definiteness of claim language must be analyzed in light of the content of the particular description in the application, and the claim interpretation that would be given by one of the ordinary skilled in the art. MPEP § 2173.02. The recitation of "blood-borne tumors" is consistent with the standard meaning commonly used by those skilled in the art. Therefore, one skilled in the art would have been able to understand the term from the disclosures of the application. Applicant respectfully requests that the rejection be withdrawn.

**The Rejection Under 35 U.S.C. §102 over Grabstald Should be Withdrawn**

Claims 23, 25-31, 33, 35-40 and 71-72 are rejected under 35 U.S.C. § 102(b) as being anticipated by Grabstald et al. (*Clin. Pharmacol. Therap.*, 1965, "Grabstald"). (Office Action, pages 6-8). Applicant respectfully traverses this rejection.

It is well settled that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (MPEP §2131, *citing Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 6315, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987)) (emphasis added).

The pending claims recite, *inter alia,* a method of treating blood-borne tumors by administering a thalidomide capsule. It is alleged that Grabstald anticipates the pending claims as it teaches administration of thalidomide to one patient having multiple myeloma. (Page 6 of Office Action).

Grabstald alleges that thalidomide was administered to 71 cancer patients. However, it does not teach a method of treating blood-borne tumors by administering a thalidomide capsule.[1] Grabstald does not teach any objective benefit of the study in multple myeloma or other blood-borne tumors. A single patient having multiple myeloma studied in Grabstald

[1] Applicant notes that only tablet formulation of thalidomide was available at the time of Grabstald study.

belonged to Series A only. (Grabstald, page 299, Table 1). Grabstald discloses that in Series A, only one patient having *renal cell carcinoma* showed objective benefit (*e.g.*, regressions of pulmonary metastases after nephrectomy[2] and the pulmonary metastases that were first noted to have disappeared in late March, 1963, did not begin to increase in size and number until October, 1963, and then they grew rapidly during the last month before death). (Grabstald, page 301, left column, last paragraph to right column, first paragraph). Grabstald concluded that "*no evidence of objective regressions* was obtained, with exception of one patient with renal cell cancer whose pulmonary metastases disappeared *transiently* after treatment. Since this patient also had a nephrectomy preceding the regression, the response may be attributed to this operation." (Grabstald, last paragraph, page 302). Therefore, Grabstald provides no evidence that the administration of thalidomide resulted in the treatment of multple myeloma or any blood-borne tumors.

The PTO's contention of anticipation is contrary to the plain disclosure of Grabstald, because the reference concludes that "no significant degree of antineoplastic activity was demonstrated....In the absence of more definite evidence of pharmacologic or anticancer effects in man, we conclude that further random trials of this drug against cancer in man are not indicated." (Grabstald, last paragraph of right column, page 301). In fact, Grabstald teaches away from Applicant's invention by demonstrating many patients did not respond. Grabstald does not teach or suggest any uses of thalidomide capsule for treating blood-borne tumors, as recited in the instant claims. Thus, Grabstald fails to disclose *each and every* limitation of the instant claims and it cannot anticipate the instant claims.

Further, Applicant's analysis of Grabstald is confirmed and supported by various articles published after the earliest filing date of this application by skilled persons in the art. Examples of the publications were previously submitted with April 19, 2007 Response, and were discussed in the May 10, 2007 Office Action. The publications confirm that (1) the interest in even trying thalidomide as a tumor therapy disappeared for about 30 years due to negative results of studies such as Grabstald, (2) it was the breakthrough made by the present inventor which demonstrated that thalidomide could be used in tumor therapy and re-ignited interest in the drug, and (3) that thalidomide is now being used and studied further as treatment for blood-borne tumors.

For example, Glasmacher, et al. (*Acta Haematol* 2005; 114 (suppl 1):3-7) discloses, on page 3, right column, line 3 from the bottom to page 4, left column, line 3, that "As early

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[2] The term "nephrectomy" means excision of a kidney, according to Dorland's Medical Dictionary, 23rd Ed., page 460.

as the 1960s, some researchers started to look at thalidomide's anti-cancer activity, but this research was quickly abandoned as the catastrophe around the drug emerged and *the first trials [including Grabstald] gave negative findings.* In the 1990s, the antiangiogenic and anti-tumor necrosis factor properties of thalidomide were explored." (emphasis underlined).

Kumar, et al. (*Journal of Clinical Oncology*, Vol. 22, No. 12, pp. 2477-2973 (2004)) reports, on page 2478, left column, lines 7-14, that "In another study *[Grabstald]*, thalidomide was evaluated in 71 patients with a variety of cancers at doses ranging from 300 to 2,000 mg/d. *Except for resolution of pulmonary metastasis in a patient with renal cell carcinoma, no other responses were seen.* There was at least one other negative study conducted during that time period. Following these initial unimpressive trials, there was little enthusiasm regarding thalidomide as an antineoplastic agent until the late 1990s." (emphasis underlined). Kumar further states that on page 2478, the second paragraph that "the resurge of interest in this drug as an antineoplastic agent in the last decade coincided with two key scientific observations....The other was *the discovery that thalidomide possessed potent antiangiogenic properties [by the present inventor D'Amato]*."

Rajkumar (*Mayo Clin Proc.* July 2004; 79(7):899-903) describes, on page 899, right column, line 6 from the bottom to page 900, left column, line 4, that "*In [Grabstald], no notable activity was seen with this drug in any of these early trials, and enthusiasm for continuing research of thalidomide as an anticancer agent disappeared for about 3 decades....thalidomide was proved unsuccessful in the treatment of cancer.*" (emphasis underlined). Rajkumar points to the present invention on page 900, the last two paragraphs "*D'Amato et al* and Kenyon et al noted that thalidomide possessed substantial antiangiogenic properties. *On the basis of evidence that antiangiogenesis was an appropriate target for cancer therapy and the fact that thalidomide possessed antiangiogenic properties, researchers at the University of Arkansas treated multiple myeloma with the drug in 1997 and thalidomide was remarkably effective in these patients.*"

Diggle (*IJCP*, November 2001, Vol. 55, No. 9, pp. 627-631) also reports on page 630, left column, the second paragraph, that "Cancer was thought to be a target for thalidomide at an early stage. In 1965 two trials of the drug *[including Grabstald]* in wide ranges of advanced malignancies were published. *The results were very disappointing, however. ... D'Amato and colleagues demonstrated the ability of the drug to inhibit angiogenesis (induced by fibroblast growth factor) in a rabbit cornea assay. This evidence was considered to justify the trial of this antiangiogenic drug in cancer again*." (emphasis underlined).

In sum, the art as a whole confirms the Applicant's analysis that Grabstald does not

anticipate the present invention of treating blood-borne tumors using thalidomide capsule, as recited in claim 23. Thus, the rejection over Grabstald must be withdrawn.

Further, Applicant notes that Office Action mailed May 10, 2007 in this application admitted that a prior art as whole including Grabstald supports that thalidomide is not effective in treating tumors in humans (pages 8-9). Also, in Office Action of February 27, 2008 issued in a divisional application no. 11/096,155, the PTO admitted that Grabstald supports that thalidomide is not effective against cancer in man (pages 4-5 and 11)[3]. Applicant respectfully submits that the PTO's contention of anticipation by Grabstald is flatly contrary to the PTO's express admission of the non-anticipation and non-obviousness of the pending claims. Therefore, as the pending claims cannot be anticipated by or obvious over Grabtald as the PTO admitted, Applicant respectfully requests that this rejection be withdrawn.

**The Rejection Under 35 U.S.C. §102 over Chen Should be Withdrawn**

Claims 23, 25-31 and 71-72 are rejected under 35 U.S.C. § 102(b) as being anticipated by Chen *et al.* (*Drug Metabolism and Disposition*, 1989, "Chen"). (Office Action, pages 9-11). Applicants respectfully traverse this rejection.

The PTO alleges that Chen teaches that the administration of thalidomide to healthy male patients, and that the patient population reads on the claim which recites "a human at risk for developing a tumor" (claim 30). Page 9 of the Office Action. Applicant respectfully traverses each of these rejections.

Claim 30 has been canceled without prejudice. The pending claims as amended recite, *inter alia,* a method of treating patients having blood-borne tumors by administering a thalidomide capsule. Chen reported on plasma pharmacokinetics and urinary excretion studies of thalidomide after oral administration to eight normal male voluteers that are in good health (page 402). However, Chen does not teach or suggest any uses of thalidomide for treating patients with blood-borne tumors, as recited in claim 23. Chen is silent as to treating blood-borne tumors with thalidomide capsule, as recited in the pending claims. Thus,

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[3] See, page 4 of the Office Action stating that [in prior art including Grabstald] "because such administration of thalidomide to humans and animals was shown to not effectively inhibit tumor growth *in vivo*, the art cannot be said to render obvious the claimed invention because there would simply be no reasonable predictability or expectation of success." Also, see, page 5 of the Office Action stating that "it was well established in the prior art that thalidomide was predominantly not effective at inhibiting tumor growth and skilled artisans in the field gave up trying to develop thalidomide for this purpose (see Grabtald *et al.*, 1965). Also, see, page 11 of the Office Action stating that *in Grabstald,* there was no evidence of an objective response in any cancer except for one patient with renal cell cancer, and the authors conclude that further random trials of this drug [thalidomide] against cancer in man are not indicated."

Chen does not teach each and every element set forth in the claim. Accordingly, the pending claims are not anticipated by Chen and this rejection must be withdrawn.

**The Rejection Under 35 U.S.C. §103 Should be Withdrawn**

Claims 59-62 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Grabstald or Chen, in view of Kaplan et al. (US Patent No. 5,385,901, "Kaplan"). (Office Action, pages 11-12). Applicant respectfully traverses this rejection.

Claims 59-62 have been canceled, and the rejection becomes moot. Further, as explained above, Grabstald and Chen teach away from the instant invention, because thalidomide was not effective in treating blood-borne tumors. For purpose of obviousness analysis, a prior art that teaches away negates an obviousness rejection. "[A]n applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." In *re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003). (Emphasis added.) Thus, Applicant respectfully submits that the instant claims are not obvious over the cited references.

Nevertheless, the Office Action states (1) that Kaplan teaches that thalidomide is useful in controlling abnormal concentrations of TNF-α; (2) that it would have been obvious to one of ordinary skilled in the art to administer thalidomide via known administration routes as thought by Kaplan. (pages 11-12 of Office Action). Applicant respectfully disagrees.

Kaplan relates to the use of thalidomide for controlling abnormal concentrations of TNF-α in Cachexia, septic shock and HIV infection (Abstract and Column 3). It does not disclose or suggest that thalidomide is useful in treating cancer, much less blood-borne tumors. Further, Kaplan teaches away from the treatment of the recited tumors by focusing on the use of the compound for treating the different diseases. Indeed, Kaplan discloses that TNF-α is associated with the destruction of tumor cells as its name suggests (Column 2, lines 60-62). Thus, a person skilled in the art would not have been motivated to use thalidomide that inhibits the TNF-α production as taught in Kaplan, for treating tumors, much less blood-borne tumors, as in the claimed invention.

In view of the foregoing, from any references cited by the Examiner, alone or in combination, one of skill in the art would have had no reason to use thalidomide capsule for treating blood-borne tumors, to arrive at the instant claims. Thus, Applicant respectfully submits that the instant claims are not obvious over the cited references.

Further, the combined teachings do not provide the legally required reasonable expectation of success. When the references are combined, one skilled in the art is merely

taught that thalidomide may be used for treating Cachexia, septic shock and HIV infection as disclosed in Kaplan, but not for treating any cancers, because Grabstald and Chen do not teach that thalidomide was effective in treating cancers, much less blood-borne tumors. As such, the art does not provide any reasonable expectation that thalidomide could be successfully used in treating blood-borne tumors. In other words, the cited art does not provide any "direction as to which of many possible choices is likely to be successful." This is precisely what the courts have held not to be a reasonable expectation of success. (*Medichem, S.A. v. Robaldo,* 437 F.3d 1157, 1165 (Fed. Cir. 2006); *O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)).

Indeed, the Office has acknowledged lack of a reasonable expectation of success and non-obviousness of the claimed invention by the art cited by the Examiner. (*P*age 4 of Office Action of February 27, 2008 issued in a divisional application no. 11/096,155 states that *[in prior art including Grabstald]* "because such administration of thalidomide to humans and animals was shown to not effectively inhibit tumor growth *in vivo*, the art cannot be said to render obvious the claimed invention because there would simply be no reasonable predictability or expectation of success." Applicant respectfully submits that the PTO's allegation that the combination of Grabstald, Chen and Kaplan obviates the instant claims is flatly contrary to the PTO's express acknowledgment of non-obviousness of the pending claims. As the PTO admitted that the pending claims cannot be obvious over the cited art, Applicant respectfully requests that this rejection be withdrawn.

## III. Conclusion

Applicant respectfully requests that the above amendment and remarks be entered in the file of this application. Should the Examiner not agree that all claims are allowable, then a further personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application. Please charge any required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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